Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

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Abstract (245 out of 250 words)

Background

Atrial fibrillation (AF) is a common cardiac condition in older adults that results in an increased risk of stroke. Antithrombotic agents decrease stroke risk associated with AF but increase bleeding risk. Falls are common in older adults and increase their bleeding risk. The purpose of this study was to determine the most cost-effective anticoagulant for older adults with AF at high risk of falling.

Methods

Using a probabilistic microsimulation Markov decision model, quality-adjusted life years (QALYs), total cost, and incremental cost-effectiveness ratios (ICERs) were calculated for each medication (ASA, warfarin, apixaban, dabigatran, rivaroxaban, and edoxaban) based on a distribution of older adults at risk of falls with atrial fibrillation. The analysis used the Ontario (Canada) public payer perspective in a lifetime horizon, and it was validated externally with published cohorts.

Results

The most cost-effective antithrombotic therapy for atrial fibrillation in older patients at risk of falls is apixaban, with an ICER of C$8,621 per QALY gained (5.92 QALYs at C$94,304) over ASA. It is a dominant strategy over warfarin and other antithrombotic agents. ASA had the lowest cost (C$86,197), but was also least effective (4.98 QALY) compared to the other medications. There was little uncertainty in the ranking with apixaban as preferred choice in 97% of model iterations.

Interpretation

From a public payer perspective, apixaban is the most cost-effective antithrombotic in older individuals at high risk of falls. Healthcare funders should implement strategies to encourage use of the most cost-effective medication in this population.

Introduction

Atrial fibrillation (AF) is a common heart dysrhythmia that increases with age [1]. AF increases stroke risk due to abnormal atrial tissue substrate and stasis from contractile dysfunction [2]. Anticoagulants are used to prevent stroke in patients with AF, but these medications increase bleeding risk [3]. AF prevalence [1], stroke risk [4], and bleeding risk [5,6] all increase with age. Furthermore, older adults are often at increased risk of falling and head injury, which can lead to serious bleeding on anticoagulation [7]. The fear of causing major bleeding leads to under-prescribing of anticoagulants in older patients, particularly those with a high risk of falling [8].

A decision analysis study published in 1999 showed that warfarin was preferred (12.90 quality-adjusted life years [QALYs]) over aspirin (11.17 QALYs) or no treatment (10.15 QALYs) for AF in those at risk of falls [9]. The more recent direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, offer generally lower bleeding risk than warfarin, but similar or lower stroke risk [10]. The DOACs are economically attractive compared to warfarin in the general population [10], but how these risks apply to an older population with falls is uncertain. Older adults with AF and falls have both higher stroke and bleeding risk, so the individual risk and efficacy of the DOACs need to be evaluated in this population.

Decision models incorporate event probabilities, trade-offs, utilities and costs to compare costs and clinical outcomes of treatment choices for a population [11]. We used a decision model to compare warfarin, aspirin, and the four DOACs for their cost-effectiveness in older adults with AF and a high risk of falls using the Ontario, Canada public health care payer perspective.

Methods

Model structure

A health state transition (Markov) model running a two-dimensional Monte Carlo simulation (microsimulation with probabilistic sensitivity analysis [12]) was constructed in TreeAge Pro 2019 (TreeAge Software Inc., Williamstown, MA) to compare the different antithrombotic agents for atrial fibrillation. Model variables were selected from distributions (outer-loop or second-order iterations) to determine the sensitivity of model output to the fact that variable estimates are measured with a degree of uncertainty, while hypothetical patients' characteristics were simulated in inner-loop (first-order) iterations. Sampling individual patient characteristics allows the probability of transition among various health states to depend on those characteristics.

The analysis involved a simulated cohort of older adults with non-valvular atrial fibrillation at high risk of falls, with distributions of age, sex, stroke risk (using CHADS score [13]), bleeding risk (using HAS-BLED score [14]), and falls risk. The base case age, sex, and falls risk distributions were derived from the Tinetti falls study (Table 1) [15], which included a cohort of older adults at risk of falls. The base case CHADS and HAS-BLED scores were derived from an AF trial population [16]. The cycle length was 3 months with a life-time time horizon. Perspective of the analysis was from the public health care system third-party payer, the Ontario Ministry of Health and Long Term Care. Discounting at 1.5% was applied to both cost and utilities based on the current Canadian Agency for Drugs and Technologies in Health

(CADTH) guidelines [17]. Within-cycle correction was used to compensate for biases occurring with discrete (non-random) Markov health transitions [18,19]. The results were reported in accordance with the CHEERS statement [20].

Strategies

The strategies included the following antithrombotic options available on the Canadian market as of January 2020:

1. Aspirin (ASA) <150mg daily
2. Warfarin titrated to INR (international normalized ratio) 2–3
3. Apixaban 5mg twice daily
4. Dabigatran 150mg twice daily
5. Rivaroxaban 20mg once daily
6. Edoxaban 60mg once daily

Clinical practice guidelines [21,22] recommend that older adults with atrial fibrillation should get an antithrombotic agent for stroke prophylaxis, so we did not simulate a "no treatment" strategy.

Outcomes

For each inner loop iteration (simulated individual), health gains were expressed as life years (LY) and quality-adjusted LY (QALYs), the latter to account for both survival and quality

of life, and costs were calculated as total lifetime costs. For both QALYs and costs, averages were computed across inner-loop iterations and, in turn, grand averages were calculated by averaging the inner loop averages across the outer loop iterations. Pairs of strategies were compared by calculating the incremental cost effectiveness ratio (ICER) as the difference in the grand averages of costs divided by the difference in grand averages of QALYs. ICERs were calculated by ranking all the strategies by lowest to highest cost. A pair of strategies consisted of a given strategy and the strategy with the next lowest cost. If the option with the higher cost had a lower effectiveness, it was considered to be directly dominated. We also considered ordered triplets of strategies to determine extended dominance. If the effectiveness of the middle strategy of a triplet could be achieved less expensively by a combination of the two neighboring strategies, the middle strategy was considered to be dominated by extension. We calculated numerical ICERs only for non-dominated strategies. The willingness-to-pay (WTP) threshold for this analysis was set at an ICER below C$50,000/QALY based on commonly accepted threshold range in Canada [23,24]. Secondary outcomes included life expectancy, cumulative major stroke, cumulative major bleeding, cumulative bedbound, and duration of time off medication.

Health states

A sample structure of the decision tree is shown in Figure 1. Simulated patients started in the "alive" health state and transitioned to the others when events were encountered (Figure 2). Stroke, bleed, and fall events were captured using tracking variables, which were used to calculate costs and utilities.

1. **Alive**: simulated patients in the "alive" health state can transition to "bedbound" state if they have a severe bleed or stroke, leading to severe disability with a modified Rankin

score of 5 [25]. Patients could also die from one of the events in the model or from other reasons based on age-adjusted mortality rates.

2. **Bedbound**: patients in the "bedbound" state remained in this state until death, but they can still experience a stroke or bleed. To simplify the model, we assumed that those who were bedbound did not experience further falls.
3. **Dead:** patients who died exited the simulation.

For adults with a major bleed, antithrombotics were discontinued for 3 months in the simulation, which is a conservative duration allowing for minimal bleeding risk [26,27]. We chose the most effective (highest) doses of each medication for the stroke prevention analysis. Patients were assumed to be adherent to the study medication with no discontinuation, but variation in adherence and effectiveness was accounted for in the model because the efficacy estimates were provided as ranges.

Model probabilities, cost and utilities

A targeted literature search (MEDLINE) was completed to obtain baseline probabilities and utilities for events related to stroke, bleeding and falls (Table 2). The baseline mortality rate for each age was derived from Statistics Canada Ontario life tables [28]. Appropriate distributions were created for each variable for outer-loop sampling. A detailed description of the model variables is available in the supplementary appendix S1.

The probability of falls, stroke (major/minor), bleed (major/minor), and mortality were derived from published trial or cohort estimates (Table 2). Drug efficacy and safety variables were obtained from a network meta-analysis comparing all medications (Table 3) [10]. Costs

related to falls, stroke, and bleed were derived from Canadian estimates [29,30]. Medication costs were obtained from the Ontario Drug Benefits Formulary and local pharmacy [31]. Indirect costs of warfarin therapy including blood monitoring and clinic visits were accounted for [32]. Cost data were adjusted for inflation to 2018 values using the Bank of Canada Consumer Price Index [33]. Utilities were derived from published estimates. All individuals entering the cohort began with the utility of having AF [34]. The utility of stroke or bleed was factored into the existing utility when those events occurred. Minor stroke, minor bleed, or a fall was associated with a disutility for a defined period of time, but not permanently.

Model Analysis

Distributions were sampled using published point estimates along with measures of variance. Variables that did not have variability (e.g. fixed costs) were inputted without distributions. The simulation for each patient terminated when death occurred or when the patient reached 100 years of age. The number of outer and inner loop iterations required for the main analysis were determined empirically according to stability of ICER and average cost estimates by running samples of different number of outer or inner loops while holding the other constant. The lowest number of outer and inner loops that resulted in stable average values was determined to be 10,000 and 5000, respectively. Residual uncertainty was explored using value of information analysis (methods and results in Supplementary appendix S2).

Model verification and validity

Face validity of the model structure and outputs were evaluated by consulting experts in cardiology (HW) and geriatric medicine (SES). The model has a similar structure as a falls and anticoagulation model published in 1999 [9]. Verification was done by two programmers that independently examined the modeling steps, checked equations and reviewed TreeAge calculations to ensure accuracy. The external validity of the model was tested by comparing secondary outcomes (cumulative falls, cumulative risk of stroke) to published cohorts. Validation results are presented in Supplementary appendix S3.

Results

LYs, QALYs, ICERs and secondary outcomes

Apixaban was associated with the greatest QALY gained, at 5.92 (Table 4). In comparison, ASA had an effectiveness of 4.98 QALY. ASA had the lowest life-time cost at C$86,197, while dabigatran had the highest cost at C$114,762. Secondary outcomes are shown in Table 5. LY and life expectancy were both longest with apixaban and shortest with ASA (7.45 vs. 6.38 LY). The proportion of patients with major stroke was lowest with dabigatran and highest with ASA (9.6% vs. 26.5%). Major bleeds occurred most frequently with dabigatran (42.8%) and least frequently with ASA (15.0%). Patients in the model spent an average of 3.49 months without medication with dabigatran vs. 1.60 months with apixaban. The proportion of patients with severe physical limitation (bedbound status) due to bleed or stroke was similar

across the medications with lowest proportions in those receiving apixaban (2.4%) or dabigatran (2.1%).

When listed by increasing life-time cost, the most economically attractive strategy was apixaban with 5.92 QALYs, and cost of C$94,304 and an ICER of C$5,036 per QALY gained compared to warfarin. Warfarin had an ICER of C$27,088 per QALY gained compared to ASA, and as such was extendedly dominated by apixaban (Figure 3). When warfarin was removed, apixaban had an ICER C$8,621 per QALY gained over ASA (Table 4). Edoxaban, rivaroxaban and dabigatran were dominated with negative ICERs and lower QALYs compared with apixaban.

When variable uncertainty was explored, apixaban was the preferred strategy in 97% of the iterations given a WTP of C$50,000 (Figure 4). ASA was the dominant strategy if the WTP threshold was below C$8,621. The incremental cost-effectiveness plots show a positive trade-off or dominance of apixaban over ASA or warfarin (Supplementary figure S2). Overall uncertainty was progressively reduced as the WTP approached C$50,000 (Supplementary figure S1).

Interpretation

This health state transition model found apixaban to be the preferred strategy for stroke prevention in older patients with AF and increased falls risk from a public payer perspective. The overall reduction in stroke and bleeding events led to a favourable QALY despite slightly higher lifetime costs of apixaban versus warfarin (C$94,304 vs. C$90,338). Apixaban had the lowest bleeding risk of all the DOACs. Since the main consequence of frequent falling is a bleeding event, it is clinically plausible that apixaban is most cost-effective.

A cost-effectiveness analysis from the United Kingdom National Health Service perspective found apixaban to be the dominant strategy for the general AF population using a WTP threshold of £20,000 [10]. Dabigatran had a lower lifetime cost overall in that study, likely due to the lower risk of bleeding in a population without falls risk. Although the original decision analysis by Man-Son-Hing et al. did not include costs [9], our findings are similar in that anticoagulation is preferred over ASA.

Our analysis builds on prior knowledge that not only is anticoagulation warranted, but apixaban is the most economically attractive choice for stroke prophylaxis in older patients with AF. The model reveals little uncertainty that apixaban is the optimal choice (Figure 4). There is little to be gained by performing more research in identifying an optimal anticoagulant for this population (Supplementary figure S1). Rather, research should be directed to implementation of the appropriate anticoagulant medication to this population, which will save cost and confer greater effectiveness over the other medications.

There are several limitations to this model. First, the model was specific to individuals who have AF at risk of falls. Simulated patients remained at elevated fall risk throughout the model despite the risk of falls decreasing after 12 months without a subsequent fall [48]. Second, individuals can only fall once per cycle, and they can no longer fall once they become bedbound. Third, patients were limited to the use of one medication in the model and assumed to be adherent to the drug. Patients could not discontinue or transition to another medication with a bleeding event, and medication compliance was not factored into the analysis. Finally, we only simulated the most effective dose (based on stroke reduction) of the medication when more than one dose was available.

Our model has a number of strengths. First, the model simulated a population of older adults at risk of falls with varying stroke and bleeding risks, in the absence of direct clinical trial evidence in this population. The model was fully probabilistic, so reasonable variations in all the model variables were tested instead of doing sensitivity analysis in only certain variables. Second, we used efficacy data from a recent systematic review and network meta-analysis that compared all of the pharmacologic treatment strategies available on the Canadian market, including ASA and warfarin. The model included the new anticoagulant edoxaban in anticipation of ODB formulary approval. Third, we included indirect costs of warfarin therapy, including bloodwork for monitoring and clinical visits, as well as Canadian cost estimates for falls, strokes and bleeds. Finally, the model was validated externally using large population cohorts.

The model provides guidance to the Ministry of Health and Long-Term Care in Ontario for which medication is ideal for older adults with AF and falls. The last study published in 2015 showed a growing trend for apixaban and rivaroxaban prescriptions in Canada for any indication [49], but more recent data are not publicly available. Future studies can investigate whether low-dose (2.5mg) apixaban will reduce bleeding risk more than the standard dose (5mg) in this population [50]. The findings from this study should be translated to policies that encourage the use of apixaban for this population over warfarin, ASA or other DOACs.

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Figure 1: Model structure.

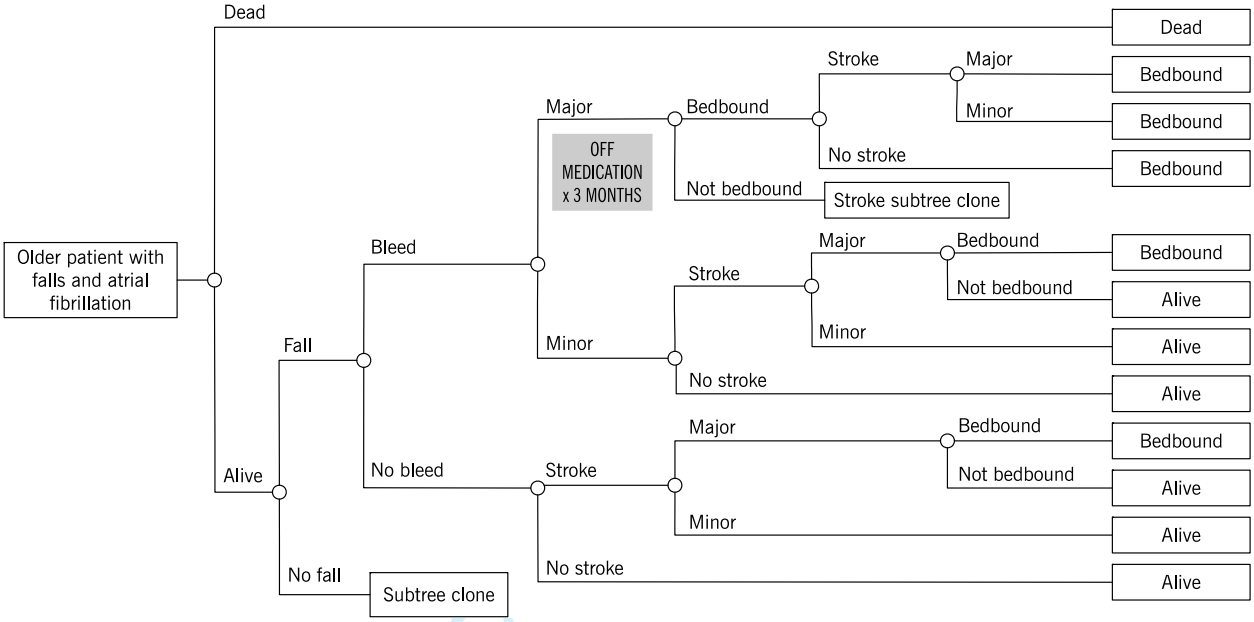


Figure 2: Health states and possible transitions.

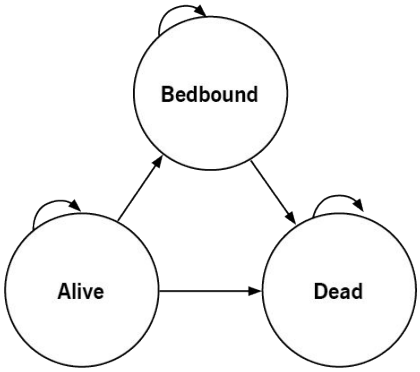


Figure 3: Average cost-effectiveness plane. The cost and effectiveness of each medication were plotted. Medications that were lower in cost (y-axis) and higher in effectiveness (x-axis) were more cost-effective. Warfarin (red circle) was dominated by extension (beige line) by the combination of apixaban (asterisk) and ASA (blue circle). QALY = quality-adjusted life years.

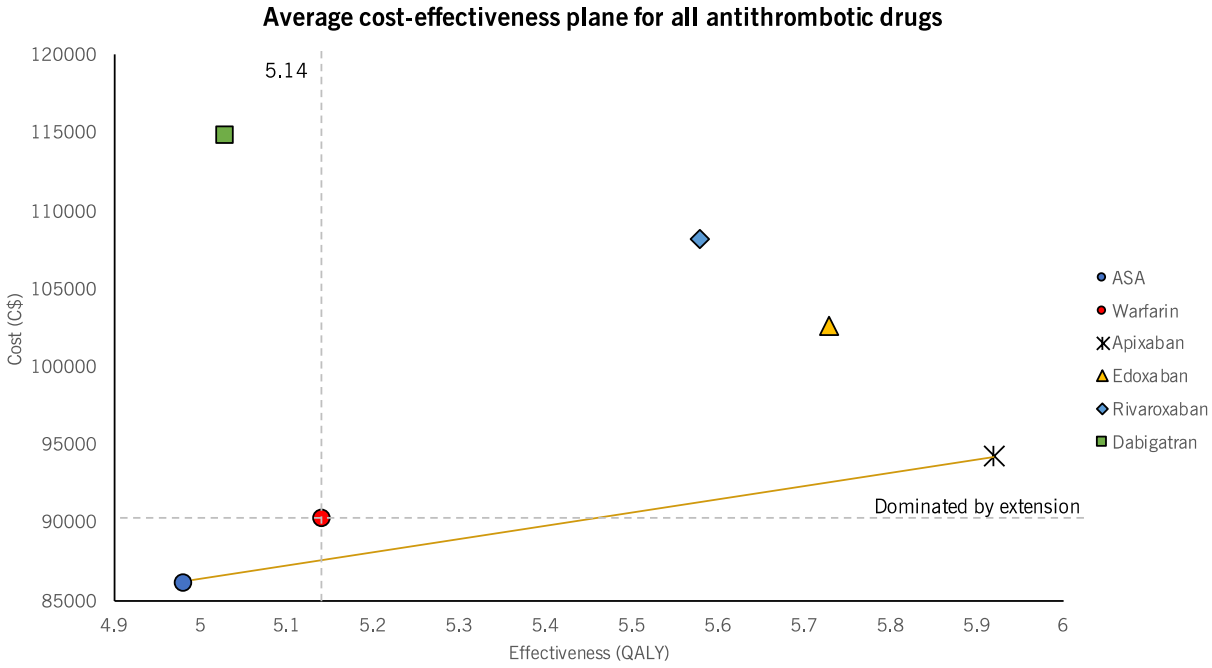


Figure 4: Cost-effectiveness acceptability curve for all antithrombotics. QALY = quality-adjusted life year.

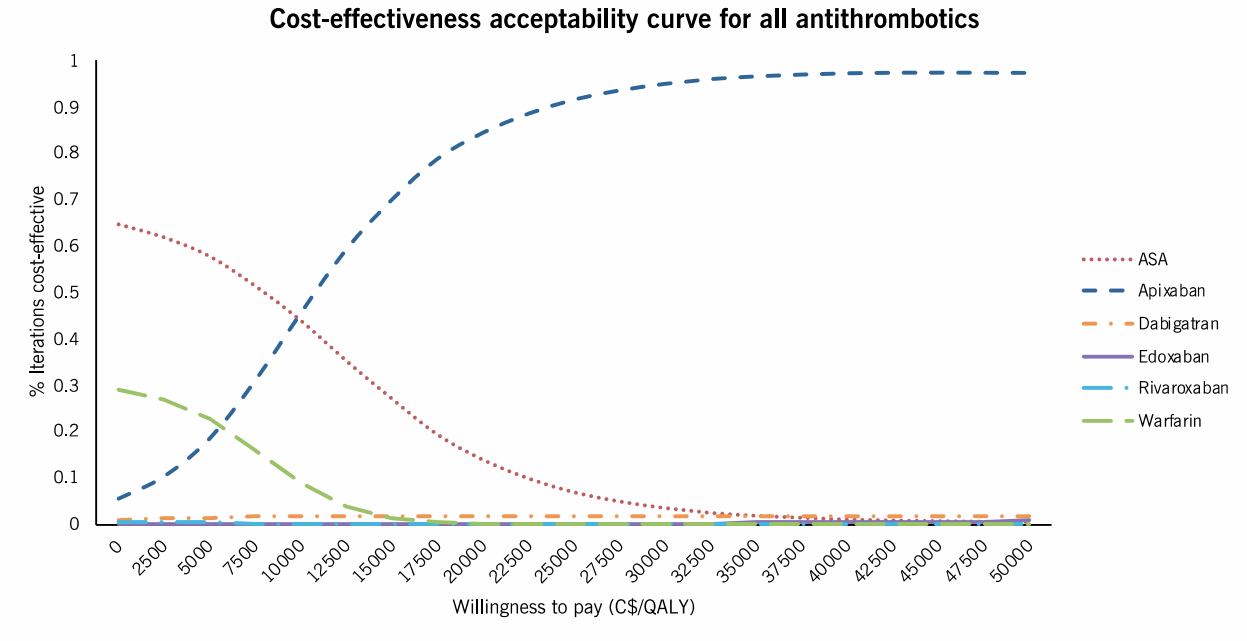


Table 1: Baseline characteristics simulated in the model. SD = standard deviation, CHADS = stroke risk score, HAS-BLED = bleeding risk score.

Age in years, mean (SD)	78.3 (5.1)	
Female	51%	
	HAS-BLED†	
CHADS*	**Low <3**	**High ≥3**
Low <3	0.58	0.19
High ≥3	0.12	0.11

*CHADS: **c**ongestive heart failure, **h**ypertension, **a**ge ≥75, **d**iabetes, and **s**troke.
†HAS-BLED: **h**ypertension, **a**bnormal renal and liver function, **s**troke, **b**leeding, **l**abile international normalized ratio, **e**lderly (age >65), **d**rugs or alcohol (≥8 drinks/week).

Table 2: Probabilities, costs and utilities for the decision model. HR = hazard ratio, HAS-BLED† = bleeding risk score, CHADS* = stroke risk score, OR = odds ratio.

	Estimate (range)	Distribution	Reference
Probabilities			
First fall	0.32 (0.27–0.37)	Beta	[15]
Subsequent fall	0.58 (0.39–0.97)	Beta	[15]
HR of bleed after a fall	1.39 (1.05–1.84)	Lognormal	[35]
Any bleed – HAS-BLED low, annual	0.166 (0.111–0.221)	Beta	[14]
Any bleed – HAS-BLED high, annual	0.091 (0.061–0.121)	Beta	[14]
Major bleed given any anticoagulant bleed	0.31 (0.25–0.46)	Beta	[36]
Intracranial bleed given major bleed	0.21 (0.14–0.28)	Beta	[37]
Bedbound after intracranial bleed (modified Rankin scale ≥5)	0.176 (0.117–0.235)	Beta	[38]
Any stroke – CHADS low	0.083 (0.055–0.111)	LogNormal	[39]
Any stroke – CHADS high	0.037 (0.025–0.049)	LogNormal	[39]
Major stroke given a stroke	0.41 (0.20–0.61)	Beta	[40]
Bedbound after major stroke (modified Rankin scale ≥5)	0.176 (0.117–0.235)	Beta	[41]
OR death due to atrial fibrillation	1.6 (1.2–2.2)	Lognormal	[42]
HR death after major stroke	5.29 (3.53–7.93)	Lognormal	[43]
HR death after major bleed	3.35 (2.12–5.27)	Lognormal	[43]
HR death given bedbound	3.81 (3.37–4.31)	Lognormal	[44]
Costs (C$ 2018 values)			
Fall, single event	7,286.01 (5,464.51–9,107.51)	Gamma	[29]
Major bleed, initial event	5,358.98 (3,572.64–7,145.28)	Gamma	[30]
Major bleeding, monthly	6,942.54 (4,627.99–9,255.99)	Gamma	[30]
Minor bleed, single event	84.38 (55.89–111.78)	Gamma	[30]
Major stroke, initial event	7,227.47 (3,613.74–14,441.79)	Gamma	[30]
Major stroke monthly	6,476.51 (4,384.7–8,768.31)	Gamma	[30]
Minor stroke, single event	3,613.74 (500.15–7,227.47)	Gamma	[30]
Bedbound (assume long-term care)	4,304.91 (2,869.94–5,739.88)	Gamma	[45]
Utilities/disutilities			
Atrial fibrillation	0.95 (0.93–0.98)	Beta	[46]
Fall, per event*	–0.11 (–0.08 to –0.14)	Beta	[47]
Major bleed, long term	0.60 (0.40–0.80)	Beta	[34]
Minor bleed, 1 month*	–0.13 (–0.08 to –0.13)	Beta	[34]
Major stroke, first year	0.26 (0.20–0.50)	Beta	[34]
Major stroke, long term	0.71 (0.40–0.96)	Beta	[34]
Minor stroke, first year*	–0.25 (–0.15 to –0.25)	Beta	[34]
Bedbound (Rankin ≥5)	0.14 (–0.01 to 0.29)	Beta	[46]
*Disutilities			

*CHADS: **c**ongestive heart failure, **h**ypertension, **a**ge ≥75, **d**iabetes, and **s**troke.
†HAS-BLED: **h**ypertension, **a**bnormal renal and liver function, **s**troke, **b**leeding, **l**abile international normalized ratio, **e**lderly (age >65), **d**rugs or alcohol (≥8 drinks/week).

Table 3: Efficacy and cost variables for antithrombotic medications. C$ = Canadian dollars in 2018 value.

	Odds ratio (95% confidence interval [CI])			
Compared to warfarin	**Any bleed**	**Any stroke**	**Death**	**Cost per month (C$)**
ASA*	0.59 (0.45–0.77)	1.88 (1.40–2.51)	1.04 (0.88–1.33)	1.02
Apixaban*	0.67 (0.60–0.75)	0.79 (0.66–0.94)	0.88 (0.79–0.98)	98.02
Dabigatran*	1.56 (0.50–5.74)	0.65 (0.52–0.81)	0.88 (0.77–1.01)	100.32
Edoxaban*	0.84 (0.77–0.90)	0.86 (0.74–1.01)	0.86 (0.82–1.01)	112.00
Rivaroxaban*	1.03 (0.95–1.11)	0.88 (0.74–1.03)	0.83 (0.69–1.00)	86.10
Warfarin	1	1	1	39.45†
Off medications‡	0.77 (0.34–1.20)	1.47 (1.29–1.65)	3.03 (2.79–3.27)	--

*Ref. [10]

‡Relative risks (95% CI). Ref. [3]

†Including cost of monitoring therapy [32]

Table 4: Cost-effectiveness ranking of the 6 different medications. Warfarin is dominated by extension by the combination of ASA and apixaban, while edoxaban, rivaroxaban and dabigatran are absolutely dominated by apixaban. All values are means with 95% confidence intervals. QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio.

Drug	Cost	Δ Cost	QALY	Δ QALY	ICER	
ASA	86,197 (85,787–86,607)	-	4.98 (4.98–4.99)	-	-	
Warfarin	90,338 (89,909–90,766)	4,141 (3,548–4,734)	5.14 (5.13–5.14)	0.15 (0.14–0.16)	27,088 (26,495–27,681)	Ext. dominated
Apixaban	94,304 (93,885–94,723)	3,966 (3,367–4,566)	5.92 (5.92–5.93)	0.79 (0.78–0.80)	5,036 (4,437–5,635)	Cost-effective
Edoxaban	102,631 (102,175–103,088)	8,327 (7,708–8,947)	5.73 (5.72–5.74)	-0.19 (-0.20 to -0.18)	-42,963 (-43,583 to -42,343)	Abs. dominated
Rivaroxaban	108,170 (107,645–108,696)	13,866 (13,194–14,538)	5.58 (5.57–5.59)	-0.34 (-0.35 to -0.33)	-40,345 (-41,017 to -39,673)	Abs. dominated
Dabigatran	114,762 (114,108–115,417)	20,459 (19,682–21,236)	5.03 (5.02–5.04)	-0.90 (-0.91 to -0.88	-22,787 (-23,564 to -22,010)	Abs. dominated

Table 5: Life years and secondary outcomes from the model. All values are means with 95% confidence intervals.

	Life years (not adjusted for utility)	Life expectancy (years)	Major strokes (cumulative %)	Major bleeds (cumulative %)	Months off medication (average per patient)	Bedbound (cumulative %)
ASA	6.38 (6.37–6.39)	84.5 (84.4–84.5)	26.5 (26.4–26.6)	15.0 (14.9–15.0)	1.19 (1.19–1.19)	4.8 (4.7–4.8)
Warfarin	6.65 (6.64–6.66)	84.7 (84.7–84.7)	14.3 (14.2–14.4)	25.9 (25.9–26.0)	2.08 (2.08–2.09)	2.7 (2.7–2.7)
Apixaban	7.46 (7.45–7.47)	85.5 (85.5–85.5)	12.7 (12.6–12.7)	19.8 (19.7–19.8)	1.60 (1.60–1.60)	2.4 (2.4–2.4)
Edoxaban	7.36 (7.35–7.37)	85.4 (85.4–85.4)	13.6 (13.6–13.7)	24.3 (24.2–24.3)	1.97 (1.96–1.97)	2.6 (2.6–2.6)
Rivaroxaban	7.31 (7.31–7.33)	85.4 (85.4–85.4)	13.9 (13.8–14.0)	29.4 (29.3–29.5)	2.39 (2.38–2.40)	2.7 (2.7–2.7)
Dabigatran	6.87 (6.86–6.89)	84.9 (84.9–85.0)	9.6 (9.5–9.7)	42.8 (42.6–43.1)	3.49 (3.47–3.51)	2.1 (2.0–2.1)

Supplementary appendix

Appendix S1: Model probabilities, cost and utilities

A targeted literature search (MEDLINE) was completed to obtain baseline probabilities and utilities for events related to stroke, bleeding and falls (Table S1). The baseline mortality rate for each age was derived from Statistics Canada Ontario life tables [1]. Appropriate distributions were created for each variable for outer-loop sampling.

The model utilized sampled patient characteristics and the validated CHADS2 [2] and the HAS-BLED [3] scoring tools to determine an individual's initial risks for stroke and bleeding while in the 'Alive' state. Patients were dichotomized into either high- or low-risk in both the CHADS2 and the HAS-BLED scores using ≥3 as cutoff for both scores. Four risk categories were created using the initial risk scores (main text Table 2), with proportions in each risk group determined from a published cohort [4]. In the 'Alive' state, patients could continue to cycle through with the possibility of dying, having a fall, or developing a stroke or a bleed. If they developed a stroke or bleed, it was stratified into a major or minor event. A major stroke or bleed was associated with a risk of permanent severe neurologic injury, defined by modified Rankin score of 5 [5,6]. Individuals with a Rankin score of 5 were transitioned to the bedbound health state, but they could experience further strokes and bleeds. Any stroke led to increased future stroke risk by increasing the CHAD2 category. Major bleeds also increased future bleeding risk (higher HAS-BLED score), but minor bleeds did not change the HAS-BLED status.

The probability of first and subsequent falls was based on the Tinetti falls cohort [7]. Each fall led to an increased risk of major bleeding, with a hazard ratio derived from an AF clinical trial that captured falls data [8]. The efficacy estimates (stroke, bleed, mortality odds ratios) for each medication are derived from a network meta-analysis (Table S1) [9]. The odds of bleeding, stroke and death of no treatment compared with warfarin was derived from a 1994 meta-analysis of the original warfarin trials for AF [10]. The no-treatment estimate was used during the period off medication after a major bleed.

Cost data was based on a previous decision analysis that utilized Canadian costs from 2013 [11]. We adjusted for inflation to 2018 values using the Bank of Canada Consumer Price Index [12]. Similarly, costs related to falls were obtained from a Canadian publication from 2009 and updated to 2018 values [13]. We also obtained costs of medications (main text Table 3) from the Ontario Drug Benefit Formulary (ODB) [14] and the St. Michael's Hospital (Toronto, Canada) outpatient pharmacy (personal communication). Indirect costs of warfarin therapy including blood monitoring and clinic visits were accounted for [15] with all costs being reported in Canadian dollars (C$). The cost of the bedbound health state was defined as requiring long-term care, and the amount paid by the Ministry of Health and Long-Term Care per month was used [16].

Utilities were derived from published estimates (Table S1). All individuals entering the cohort began with the utility of having AF [17]. The utility of stroke or bleed was factored into the

existing utility when those events occurred. Minor stroke, minor bleed, or a fall was associated with a disutility for a defined period of time, but not permanently.

Table S1: Full variable set including distributions and sampling iteration. Log normal distribution parameters were mean of logs and standard deviation of logs. IL = inner loop (first order), OL = outer loop (second order), μ = mean, σ = standard deviation, HR = hazard ratio, OR = odds ratio.

	Sampled iterations	Distribution parameters	Reference
Baseline characteristics			
Starting age	IL	Normal (μ=78.3, σ=5.1)	[7]
Sex female	IL	Uniform (<0.51)	[7]
Start CHADS/HAS-BLED profile	IL	Uniform (0–0.58, 0.58–0.77, 0.77–0.89, 0.89–1)	[4]
Probabilities			
First fall	IL	Beta (μ=0.32, σ=0.025)	[7]
Subsequent fall	IL	Beta (μ=0.58, σ=0.097)	[7]
HR of bleed after a fall	OL	LogNormal (μ=0.329, σ=0.122)	[8]
Any bleed – HAS-BLED low, annual	IL	Beta (μ=0.166, σ=0.055)	[3]
Any bleed – HAS-BLED high, annual	IL	Beta (μ=0.091, σ=0.030)	[3]
Major bleed given any anticoagulant bleed	OL	Beta (μ=0.31, σ=0.03)	[18]
Intracranial bleed given major bleed	OL	Beta (μ=0.21, σ=0.07)	[19]
Bedbound after intracranial bleed (modified Rankin scale ≥5)	IL	Beta (μ=0.176, σ=0.059)	[6]
Any stroke – CHADS low	IL	LogNormal (μ=–3.297, σ=0.325)	[20]
Any stroke – CHADS high	IL	LogNormal (μ=–2.489, σ=0.325)	[20]
Major stroke given a stroke	OL	Beta (μ=0.41, σ=0.11)	[21]
Bedbound after major stroke (modified Rankin scale ≥5)	IL	Beta (μ=0.176, σ=0.059)	[5]
OR death due to atrial fibrillation	OL	Lognormal (μ=0.470, σ=0.125)	[22]
HR death after major stroke	OL	Lognormal (μ=1.666, σ=0.246)	[23]
HR death after major bleed	OL	Lognormal (μ=1.209, σ=0.281)	[23]
HR death given bedbound	OL	Lognormal (μ=1.337, σ=0.125)	[24]
Costs (C$ 2018 values)			
Fall, single event	OL	Gamma (μ=7,286.01, σ=2,428.67)	[13]
Major bleed, initial event	OL	Gamma (μ=5,358.98, σ=1,786.33)	[11]
Major bleeding, monthly	OL	Gamma (μ=6,942.54, σ=2,314.18)	[11]
Minor bleed, single event	OL	Gamma (μ=84.38, σ=28.13)	[11]
Major stroke, initial event	OL	Gamma (μ=7,227.47, σ=2,409.16)	[11]
Major stroke monthly	OL	Gamma (μ=6,476.51, σ=2,158.84)	[11]
Minor stroke, single event	OL	Gamma (μ=3,613.74, σ=1,204.58)	[11]
Bedbound (assume long-term care)	OL	Gamma (μ=4,304.91, σ=1,434.97)	[16]
Utilities/disutilities			
Atrial fibrillation	IL	Beta (μ=0.95, σ=0.02)	[25]
Fall, per event*	IL	Beta (μ=–0.11, σ=0.04)	[26]
Major bleed, long term	IL	Beta (μ=0.31, σ=0.03)	[17]
Minor bleed, 1 month*	IL	Beta (μ=0.21, σ=0.07)	[17]
Major stroke, first year	IL	Beta (μ=0.176, σ=0.059)	[17]
Major stroke, long term	IL	LogNormal (μ=–3.297, σ=0.325)	[17]
Minor stroke, first year*	IL	LogNormal (μ=–2.489, σ=0.325)	[17]
Bedbound (Rankin ≥5)	IL	Beta (μ=0.41, σ=0.11)	[25]
*Disutilities			

Supplementary appendix: Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

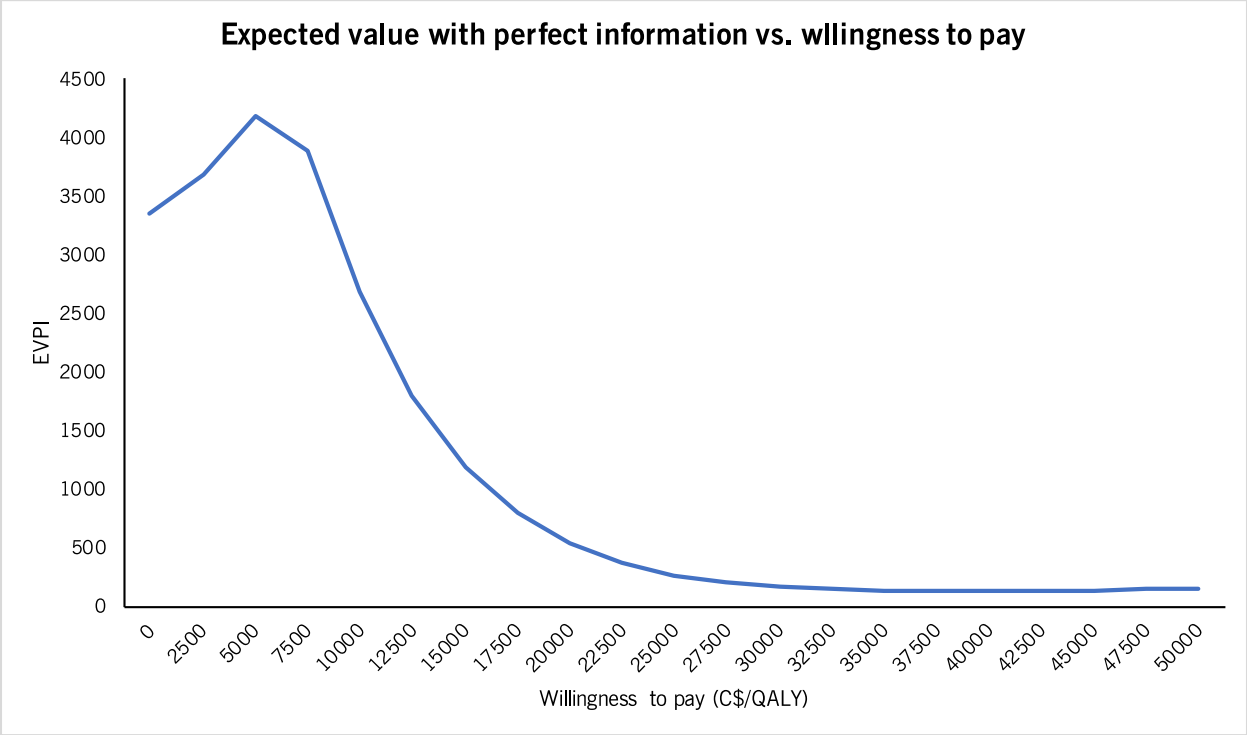
Drug efficacy and safety			
ASA, OR any bleed	OL	LogNormal (μ=–0.528, σ=0.137)	[9]
ASA, OR any stroke	OL	LogNormal (μ=0.631, σ=0.149)	[9]
ASA, OR death	OL	LogNormal (μ=0.039, σ=0.105)	[9]
Apixaban, OR any bleed	OL	LogNormal (μ=-0.400, σ=0.057)	[9]
Apixaban, OR any stroke	OL	LogNormal (μ=-0.236, σ=0.090)	[9]
Apixaban, OR death	OL	LogNormal (μ=-0.128, σ=0.055)	[9]
Dabigatran, OR any bleed	OL	LogNormal (μ=0.445, σ=0.623)	[9]
Dabigatran, OR any stroke	OL	LogNormal (μ=-0.431, σ=0.113)	[9]
Dabigatran, OR death	OL	LogNormal (μ=-0.128, σ=0.069)	[9]
Edoxaban, OR any bleed	OL	LogNormal (μ=-0.174, σ=0.040)	[9]
Edoxaban, OR any stroke	OL	LogNormal (μ=-0.151, σ=0.079)	[9]
Edoxaban, OR death	OL	LogNormal (μ=-0.151, σ=0.053)	[9]
Rivaroxaban, OR any bleed	OL	LogNormal (μ=0.030, σ=0.040)	[9]
Rivaroxaban, OR any stroke	OL	LogNormal (μ=-0.128, σ=0.084)	[9]
Rivaroxaban, OR death	OL	LogNormal (μ=-0.186, σ=0.095)	[9]
Off medication, OR any bleed	OL	LogNormal (μ=-0.262, σ=0.325)	[10]
Off medication, OR any stroke	OL	LogNormal (μ=0.386, σ=0.117)	[10]
Off medication, OR death	OL	LogNormal (μ=1.109, σ=0.443)	[10]

Supplementary appendix: Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

Appendix S2: Value of information (VOI) analysis

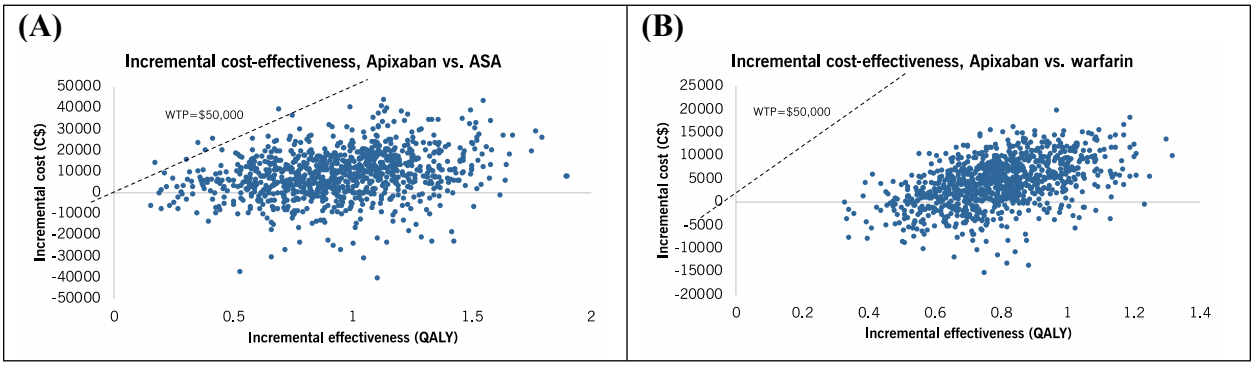
Residual uncertainty of the model was explored using VOI analysis [27]. The expected value with perfect information (EVPI) is derived from the difference of the model estimate and expected values with no uncertainty (perfect information). The EVPI was plotted against willingness to pay (WTP) in Figure S1. EVPI gives an estimate of opportunity costs (potentially lost costs) with the current level of evidence. If the cost of new evidence is less than the EVPI, then studies should be done to further reduce uncertainty in the model. In this model, the EVPI progressively decreases to near 0 as WTP approaches C$50,000/QALY, suggesting that there is minimal uncertainty with the results found.

Figure S1: Expected value with perfect information (EVPI) vs. willingness-to-pay (WTP).



Supplementary appendix: Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

Figure S2: Incremental cost-effectiveness plots for (A) apixaban vs. ASA and (B) apixaban vs. warfarin.



Supplementary appendix: Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

Appendix S3: Model validation results

Using the prespecified variables, the model was shown to be externally valid. The cumulative number of falls in the model was 4.17 (95% confidence interval, CI 3.41–4.94) compared with 3.59 in a United States population-based cohort [28] and 6.57 in a Finnish geriatric community-dwelling cohort [29]. The cumulative number of falls was determined by multiplying the annual falls rate by the average life years from the model. The cumulative stroke risk in the model with ASA is 0.26 (0.13–0.40). The Framingham cohort estimates the cumulative stroke risk from age 75 to be 0.104 [30]. Adjusting for the presence of AF (relative risk, RR 3.3 from the Framingham cohort [31]) and the risk reduction with ASA (RR 0.64 [10]), the cumulative stroke risk is 0.22, which is similar to the model estimate. No calibration was required.

Supplementary appendix: Cost-effectiveness of antithrombotic agents for atrial fibrillation in older adults at risk of falls

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